UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RALPH H. WEICHSELBAUM,
DENNIS E. HALLAHAN,
DONALD W. KUFE and
VIKAS P. SUKHATME

Appeal No. 2006-0141
Application No. 08/289,290[1]
Technology Center 1600

Decided: February 12, 2007

Before LORIN, SCHEINER, and DELMENDO, Administrative Patent Judges.

LORIN, Administrative Patent Judge.

DECISION ON APPEAL

STATEMENT OF THE CASE

Claims 1-3, 6, 8-14, 18-22, 26-29, and 31-42 are currently pending. The '290 application was previously before the Board for a decision on appeal (1999-1365, mailed 14 March 2002) from a final rejection of claims 1-3, 6, 8-14, 17-22, and 26-36, all claims then pending in the application. Claims 37-42 were added

[1] Filed 11 August 1994. The real party in interest is ARCH Development Corporation.

subsequent to the prior Board decision. Claims 1-3, 6, 8-14, 18-22, 26-28, 31-36, 38, 39, 41 and 42 are now indicated as allowable. Answer, p. 3. Claims 17 and 30 are now cancelled. Brief, p. 2.

Claim 40 was finally rejected under 35 U.S.C. § 112, first paragraph (Answer, p. 3) and appellants appealed that rejection (Brief, p. 9). However, as the Reply (p. 2) indicates, claim 40 has been amended (7 March 2005) and as a consequence the examiner (communication of 3 June 2005) has withdrawn the sole rejection of claim 40 under 35 U.S.C. § 112, first paragraph. Accordingly, the appeal of claim 40 is dismissed as moot.

Thus, claims 29 and 37 are the only claims involved in this appeal.

The decision of the Primary Examiner rejecting claims 29 and 37 of Application 08/289,290 ("the '290 application") over prior art is appealed. 35 U.S.C. § 134 (2002). We have jurisdiction to review the adverse decision of the examiner under 35 U.S.C. § 6 (b) (2000).

We AFFIRM.[2]

Appellants (Brief, pp. 4-5), state that claims 29 and 37 do not stand or fall together but, with respect to the appealed rejection (Brief, pp. 8-9), appellants argue the claims as a group. The Board selects representative claim 29 to decide the appeal as to all the finally rejected claims. 37 CFR § 41.37(c)(1)(vii).

Claims 29 reads as follows:

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[2] Our decision will make reference to appellants' Second Corrected Brief On Appeal ("Brief," filed 24 May 2004), the examiner's Answer ("Answer," mailed 19 January 2005), and appellants' Reply To Examiner's Answer ("Reply," 10 March 2005).

29. A pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle.

ISSUES

Would one of ordinary skill in the art reading Zhang and Walther arrive at the claimed composition with a reasonable expectation of success so that claims 29 and 37 would have been obvious to one of ordinary skill in the art under 35 U.S.C. § 103(a) over Zhang and Walther?

FINDINGS OF FACT

The following findings of fact ("FF") are believed to be supported by at least a preponderance of the evidence. To the extent any finding is a conclusion of law, it may be treated as such.

1. The examiner (see Answer, p. 7) finally rejected claims 29 and 37 of the '290 application as being unpatentable under 35 U.S.C. § 103(a) as being obvious over Zhang in view of Walther.

2. Claim 29 is drawn to a pharmaceutical composition comprising two components: (a) a genetic construct comprising a nucleic acid encoding a tumor necrosis factor alpha (TNF-α) and (b) an adenovirus particle.

3. U.S. Patent 6,143,290 ("Zhang") issued on 7 November 2000 on an application filed on 7 April 1994.[3]

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[3] Zhang qualifies as prior art as to the claims of the '290 application by virtue of 35 U.S.C. § 102(e). Appellants do not dispute Zhang's qualifications to be prior art as to the claims of the '290 application.

4. Walther at al., Anticancer Research 13: 1565-1574 (1993), Retrovirus-Mediated Gene Transfer of Tumor Necrosis Factor Alpha into Colon Carcinoma Cells Generates a Growth Inhibition ("Walther") was published in 1993.[4]

5. The examiner (Answer, p. 7) correctly states that "[Zhang] teach[es] an adenovirus construct comprising a nucleic acid that encodes a tumor suppressor gene p53 ... ." See Zhang (column 3, lines 46-49), which states:

> The invention therefore concerns adenovirus vector constructs that involve using Adenovirus to carry tumor suppressor genes such as p53, anti-sense oncogenes and other related genes for human cancer therapy.

6. Zhang (column 1, lines 63-65) discloses that the gene encoding the p53 protein is a tumor suppressor gene that controls cell proliferation.

7. The examiner correctly states that Zhang teaches a constitutive promoter controlling the p53 expression region. See Zhang (column 3, lines 63-66), which states:

> In preferred embodiments, it is contemplated that one will desire to position the p53 expression region under the control of a strong constitutive promoter such as a CMV promoter, ...

8. The examiner correctly states that Zhang teaches an adenovirus construct in a pharmaceutically acceptable carrier. See Zhang (column 5, lines 1-4), which states:

> Other embodiments concern pharmaceutical compositions comprising a recombinant adenovirus which encodes wild type p53, dispersed in a pharmacologically acceptable solution or buffer.

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[4] Walther qualifies as prior art as to the claims of the '290 application by virtue of 35 U.S.C. § 102(a). Appellants do not dispute Walther's qualifications to be prior art as to the claims of the '290 application.

9. Appellants (Brief, p. 8) do not dispute the examiner's findings of what Zhang teaches.

10. The examiner states that the subject matter of claim 29 differs from Zhang's teachings only in that Zhang teaches a genetic construct comprising a nucleic acid encoding a tumor suppressor p53 and not a nucleic acid encoding tumor necrosis factor alpha (TNF-α) as claim 29 requires.

> The teaching of [Zhang] differs from [the] instant[ly] claimed [subject matter] in that [it] discloses an adenoviral vector comprising a nucleic acid that encodes a tumor suppressor p53, not TNF-α.

Answer, p. 8.

11. Appellants (Brief, p. 8) do not dispute the examiner's findings as to the difference between the gene constructs of claim 29 and Zhang.

12. The examiner relies on Walther to show that it was well known in the art to form a genetic construct comprising a nucleic acid that encodes TNF-α.

> [Walther] ... establish[es] that it is well known in the art [that] a gene therapy vector could be used for encoding and expressing a nucleic acid that encodes TNF-α for the treatment of tumor. [Walther] teach[es] a genetic construct comprising a nucleic acid that encodes TNF-α packaged in a retrovirus particle (paragraph bridging page 1565-66, and 2nd paragraph in left column of 1956).

Answer, p. 8.

13. Walther (p. 1565) discloses that TNF-α is an anti-tumor cytokine that decreases cell proliferation.

14. Appellants (Brief, p. 8) agree with the examiner that "[Walther] discloses the introduction of a retroviral vector encoding the TNF-α gene to tumor cells ...."

15. Accordingly, there is no dispute that (a) Zhang discloses an adenovirus construct which may be used to carry genes for cancer therapy other than p53 and (b) Walther discloses a retroviral construct used to carry a gene expressing TNF-α. The table below summarizes the key differences between the prior art and the claimed invention (i.e., Zhang teaches one and Walther the other component of the claimed composition).

	Zhang	Walther	Claim 29
Nucleic Acid	encodes p53	encodes TNF-α	encodes TNF-α
Vector Construct	adenovirus	retrovirus	adenovirus

16. The examiner concedes that "[Walther] do[es] not teach an adenoviral vector" (Answer, p. 8).

17. However, the examiner (Answer, p. 8) states that "[a]lthough Walther et al do not teach an adenoviral vector, the vector and the need to use it in place of retroviral vector was taught in Zhang et al."

18. Zhang discusses problems associated with using a retroviral construct to carry genes for human cancer therapy, suggesting the use of adenoviral vectors. See Zhang (column 2, lines 30-43):

> Gene delivery systems applicable to gene therapy for tumor suppression are currently being investigated and developed. ... Some progress has been made in this regard as, for example, in the generation of retroviral vectors engineered to deliver a variety of genes. However, major problems are associated with using retroviral vectors for gene therapy since their infectivity depends on the availability of retroviral receptors on the target cells, they are difficult to concentrate and purify, and they only integrate efficiently into replicating cells.

19. The examiner (Answer, p. 9) contends that one of ordinary skill in the art would modify Zhang's adenoviral vector to substitute the tumor suppressor gene

taught therein, such as p53, with a gene expressing TNF-α in view of Walther's teaching that TNF-α suppresses tumors, and arrive at the claimed subject matter with a reasonable expectation of success.

20. Appellants (Brief, p. 9) contend that one of ordinary skill would need to use hindsight to modify Zhang in view of Walther and arrive at the claimed invention.

21. Appellants argue that Zhang ("(see, e.g., column 14, lines 30-35)," Brief, p. 8) discloses a decrease in p53 expression when using an adenoviral construct.

22. Zhang (column 3, lines 6 – column 4, lines 59) discloses a particular p53-adenovirus construct under the control of the human cytomegalovirus promoter (Ad5CMV-p53) which "mediated a high level of expression of the p53 gene in human lung cancer cells" (column 14, lines 19-20) and showed a "duration of [wild-type] p53 expression after infection [of] more than 15 days in H358 [lung cancer] cells" (column 14, lines 29-30). "[A] rapid decrease in expression after postinfection day 5" (column 14, lines 30-31) was also shown, the possible result of "cellular attenuation of the CMV promoter that controls p53 expression" (column 14, lines 36-38).

23. Zhang (column 14, lines 50-54) states:

> The short-term high level expression of the wild-type p53 protein observed in the present study may have the beneficial effect of reducing possible side-effects on normal cells following in vivo treatment with Ad5CMV-p53.

24. The claims do not limit the claimed nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter to a particular level and duration of expression.

25. Appellants (Brief, p. 8) argue that Walther discloses [reduced] tumor growth inhibition when retrovirally-encoded TNF-α is constitutively expressed.

26. Walther (p. 1572, left column) suggests that tumor growth inhibition may be due to a particular amount of expressed TNF.

27. Walther (p. 1572, left column) discloses that "construction of retroviral expression vectors with promoters of different lengths" may affect TNF-α expression and tumor progression.

28. Walther (p. 1572, left column) indicates that (unpublished) data shows "[u]sing the cytomegalovirus (CMV) immediate promoter to drive the TNF expression in LS174T [colon carcinoma cells resistant to external addition of TNF] ... [produced] amounts of biologically active TNF between 200 and 1000 pg/ml [with a] the growth inhibitory effect [that] was significantly lower in comparison to the LTR-promoted cytokine expression". Emphasis added.

29. The claims do not limit the type of constitutive promoter.

PRINCIPLES OF LAW

1. The examiner bears the initial burden of presenting a prima facie case of obviousness under 35 USC § 103. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

2. "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Id." In re Vaeck, 947 F. 2d 488, 493 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

3. A prima facie case of obviousness is established by presenting evidence that would have led one of ordinary skill in the art to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) and In re Lintner, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

ANALYSIS

We find that the examiner has met the initial burden of establishing a prima facie case of obviousness.

Zhang discloses an adenovirus construct which may be used to carry genes for cancer therapy. FF 5. Among the genes which Zhang discloses may be carried by the adenovirus construct are "tumor suppressor genes such as

p53, anti-sense oncogenes and other related genes for human cancer therapy." FF 5. (Emphasis added.)

Walther discloses a retroviral vector construct, rather than an adenovirus construct, to carry a gene encoding TNF-α. The gene encoding TNF-α that Walther discloses is useful for human cancer therapy. FF 12-13.

The only difference between Walther and the claimed subject matter is that Walther uses a retroviral vector while the claimed construct uses an adenoviral vector.

Zhang discloses that employing an adenovirus vector rather than retroviral vectors where retroviral vectors are used for gene therapy overcomes problems associated with retroviral vectors. Zhang (column 2, lines 30-43, FF 2.) states:

> Gene delivery systems applicable to gene therapy for tumor suppression are currently being investigated and developed. ... Some progress has been made in this regard as, for example, in the generation of retroviral vectors engineered to deliver a variety of genes. However, major problems are associated with using retroviral vectors for gene therapy since their infectivity depends on the availability of retroviral receptors on the target cells, they are difficult to concentrate and purify, and they only integrate efficiently into replicating cells.

(Emphasis added.) To one of ordinary skill in the art reading Zhang, Walther's delivery of the gene encoding TNF-α for human cancer therapy would be improved if the retroviral vector that Walther uses in its gene construct was replaced by an adenovirus vector.

Furthermore, Zhang discloses that the adenovirus construct may be used to carry genes for human cancer therapy. FF 5. The gene expressing TNF-α is a gene for human cancer therapy. FF 12-13. One of ordinary skill in the art

reading Zhang, would reasonably expect that an adenovirus construct could carry the gene expressing TNF-α and be applicable in human cancer therapy. One of ordinary skill in the art reading Zhang would reasonably expect an adenovirus construct for delivering the gene expressing TNF-α for human cancer therapy to be an improvement over a retroviral vector for doing the same (i.e., Walther).

Zhang provides sufficient motivation to arrive at the claimed invention with a reasonable expectation of success given the disclosures of Zhang and Walther.

The examiner has established a prima facie case of obviousness by presenting evidence (i.e., Zhang and Walther) that would have led one of ordinary skill in the art to combine the relevant teachings of the references to arrive at the claimed invention.

Appellants' contend that one of ordinary skill would need to use hindsight to modify Zhang in view of Walther to arrive at the claimed invention. FF 20.

Appellants argue that Zhang discloses a decrease in p53 expression when using an adenoviral construct. FF 21. The disclosure in Zhang to which appellants refer describes a particular p53-adenovirus construct under the control of the human cytomegalovirus promoter (Ad5CMV-p53). FF 22. Although "a rapid decrease in expression after postinfection day 5" (column 14, lines 30-31) was shown (the possible result of "cellular attenuation of the CMV promoter that controls p53 expression" (column 14, lines 36-38)), it nevertheless "mediated a high level of expression of the p53 gene in human lung cancer cells"

(column 14, lines 19-20) and showed a "duration of [wild-type] p53 expression after infection [of] more than 15 days in H358 [lung cancer] cells" (column 14, lines 29-30). FF 22. The principle set forth in Zhang that the p53-adenovirus construct is useful for gene therapy is not diminished by the disclosure of "a rapid decrease in expression after postinfection day 5" because even with the Ad5CMV-p53 construct a high level of expression of the p53 gene in human lung cancer cells and expression lasting at least 15 days was observed. Moreover, the instant claims do not limit the degree or duration of gene expression and therefore read on constructs useful in cancer therapy which may over time show decreased expression. In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) ("A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.")

Appellants also argue that Walther discloses reduced tumor growth inhibition when retrovirally-encoded TNF-α is constitutively expressed. FF 25. Walther (p. 1572, left column) suggests that reduced tumorigenicity may be due to low amounts of expressed TNF. FF 26. Walther (p. 1572, left column) discloses that "construction of retroviral expression vectors with promoters of different lengths" may affect TNF-α expression and tumor progression. FF. 27. Walther (p. 1572, left column) discloses that (unpublished) data shows "[u]sing the cytomegalovirus (CMV) immediate promoter to drive the TNF expression in LS174T [colon carcinoma cells resistant to external addition of TNF] ... [produced] amounts of biologically active TNF between 200 and 1000 pg/ml [with

a] the growth inhibitory effect [that] was significantly lower in comparison to the LTR-promoted cytokine expression" (emphasis added). FF 28. Accordingly, Walther suggests that reduced tumor inhibition is the result of using the cytomegalovirus (CMV) immediate promoter to drive the TNF expression in LS174T. The principle set forth in Walther that the TNF-retrovirus construct is useful for gene therapy is not diminished by this because even with the use of the cytomegalovirus (CMV) immediate promoter to drive the TNF expression in LS174T, expression of TNF-α was observed. Moreover, the instant claims do not limit the type of constitutive promoter and therefore read on constructs using a constitutive promoter which, though driving the TNF expression, may do so at a decreased level.

Neither argument is persuasive in showing that the examiner used impermissible hindsight in rejecting the claims over the prior art.

CONCLUSION OF LAW

On the record before us, appellants have failed to show that the examiner erred in rejecting the claims over the prior art. The examiner's evidence and rationale is sufficient to make out a prima facie case of obviousness of the claims under 35 U.S.C. § 103(a) over Zhang and Walther.

Appellants have not sustained their burden of overcoming the prima facie case made out by the Examiner.

DECISION

The examiner's rejection of claims 29 and 37 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). See 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

HCL/jrg

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